IPEC Americas and Europe Excipient Pedigree Position Paper

In 1998 as a result of a tragedy in Haiti and similar earlier cases, the World Health Organization (WHO) initiated the development of Guidelines for Good Trade and Distribution Practices (GDTP). Subsequently the International Pharmaceutical Excipient Council of the Americas (IPEC - Americas) prepared a white paper on the Qualification of Excipient Vendors which was published as an editorial[1]. Since then TriPEC (IPEC – Americas and Europe, and JPEC) has published and initiated the development of numerous guidelines concerning such subjects as Good Manufacturing Practices (GMPs), Good Distribution Practices (GDPs), Certificates of Analysis (COAs), Notification of Significant Change, and has initiated the development of a guideline detailing how manufacturers and users qualify pharmaceutical grade Excipients. Unfortunately, in spite of these efforts, which were not designed to detect fraud, tragedy struck again in China and Panama in 2006. These incidents were similar to the one in Haiti which again demonstrated the obligation of pharmaceutical dosage form manufacturers to know the complete supply chain of the excipients they use. In other words they must know the "Excipient Pedigree".

This position paper is published as a guide for determining, documenting, and verifying the complete supply chain history of an excipient. Its objective is to describe a process and its elements that will establish the pedigree of an excipient with a high degree of confidence using existing documentation to the greatest extent possible. This effort is intended to act as a further deterrent to fraud and will require the full cooperation of all the parties involved in the supply chain, i.e. excipient manufacturers, distributors, and users.

For the purpose of this document "distributors" includes all parties involved in trade and distribution, (re)processors, (re)packagers, transport and warehousing companies, forwarding agents, brokers, traders, and any additional suppliers other than the original excipient manufacturer. It is recommended that the principles contained herein should be integrated into the quality system of those companies involved in the supply chain.

EXCIPIENT MANUFACTURERS are expected to follow current IPEC-PQG GMP and GDP Guidelines during the manufacture, handling, packaging, testing, storage and shipping of an excipient and to supply a COA in accordance with the relevant IPEC Guideline. If the excipient is to be supplied via a distributor, its manufacturer should confirm, upon request, that the material was shipped to the distributor.

In addition, if the excipient is to be supplied via distributors, it is recommended that all distributors in the supply chain follow established Good Distribution principles as published by the WHO and IPEC. Excipient manufacturers should periodically audit or use a qualified third party auditor to audit their distributors to ensure that appropriate quality systems are documented and effective as well as to confirm that traceability and cross contamination control are implemented throughout the entire supply chain. The IPEC Good Distribution Practices Guide for Pharmaceutical Excipients should be used as the basis for such audits.

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[1] A.J. Falk, "Qualification of Excipient Vendors", Guest Editorial, *Pharm. Tech*. April 1998, 12

THE DISTRIBUTOR should comply with the IPEC GDP Guide. In addition, the distributor should provide to the user, upon request, a record of the chain of custody for the excipient by using existing documents such as bills of transfer with the financial data redacted. In all instances, the distributor must provide a COA for each delivery. This may be a copy of the COA from the original excipient manufacturer or, where appropriate, the distributor's own COA. This must be based on their own analytical testing results and must include, as recommended by the IPEC COA Guide, the identity and location (including country) of the manufacturer. If the distributor repackages the material, they must appropriately sample, analyze, and include these results in their own COA. There must be traceability and the ability to recall material. It is recommended that excipient manufacturers and distributors conduct mock recalls to test the effectiveness of their recall procedure.

If a distributor receives material into a holding tank, only materials from the same excipient manufacturer's site or terminal and conforming to the same specifications can be mixed The distributor that loads or packages from bulk excipient should follow the WHO GTDP and IPEC GDP principles regarding definition of batches, analysis of the material and preparation of the COA.

Finally, the distributor should have an effective change management program in operation, including notification to their customers as appropriate and in accordance with the Significant Change Guide[2].

THE USER bears the responsibility for all excipients used and therefore must know the origin and complete supply chain for each batch (excipient pedigree) of each material. Apart from performing appropriate testing of each incoming excipient lot, the user should audit both the excipient manufacturer and the distributor, or use a qualified third party auditor using the appropriate IPEC Guides as the basis. This responsibility to audit extends to other distributors in the supply chain where appropriate. Information on excipients shipped to distributors early in the supply chain may be obtainable from the excipient manufacturer. In addition to auditing, the user should verify on a periodic basis the chain of custody (described above). All this should be completed as part of qualifying the supply chain of the excipient.

Labeling material as compendia material solely based upon test results remains a significant problem in the excipient market. Non-GMP material (e.g., Technical Grade) must never be relabeled as compendia grade based solely on conformance to the compendia monograph. The original material must have been manufactured, tested, stored, repackaged (if performed), and relabeled (if performed) in conformance to appropriate excipient GMP requirements.

The process described above will work only if all parties involved in the supply chain from the manufacturer through the distributor(s), to the user are willing to share records that establish excipient pedigree and take responsibility for the safety of the patient.

[2] IPEC-Americas Significant Change Guide